IN PROFILE

An in-depth view of an organization or individual involved in thalassemia

In this issue, we bring you excerpts from an interview with β-thalassemia patient NinaMaria Badalamenti, a 26 year old news producer living in Indianapolis, United States.

‘Growing up with thalassemia’ involved a lot of hospital visits, a lot of tests, surgery and regular transfusions. I’ve been blessed with a really good care team that I’ve had pretty much my whole life. I missed some school and that was kind of hard – kids started to notice. So it was a little bit of a struggle for a while. But my parents instilled in me that thalassemia wasn’t going to hold me back. And that you go on and live a normal life, just have the mindset that I can be normal, I can do anything. I just need to do what the doctor recommends, and take care of my health.’

‘I’ve been transfusion dependent my whole life. Most of my childhood, it was every three weeks that I got a transfusion. Now I’m up to every four weeks, but that’s kind of my max. We’ve learned a good balance and what I need to get through those four weeks.’

‘It’s been challenging figuring out when and how to explain thalassemia to others. Especially growing up, kind of keeping it to myself. It’s been a little bit scary. But what I’ve learned is to just let it happen naturally and not to be ashamed. Most of the time people are intrigued, they’re interested. It’s something that I’m finally able to do comfortably.’

‘I’ve learned that I’m a lot stronger and more capable than I ever thought I was. I’ve allowed thalassemia to be something that gives me strength.’

‘I’d advise anyone new to thalassemia not to be ashamed – everyone has something and this is your thing. Most people are a lot more accepting than you think they’re going to be. Secondly, take your health in your own hands. So find a good care team, find a good doctor and listen to them. And also, know your own health, you know your body more than anyone else. So you need to listen to it and work with your doctor to live your fullest life and not allow it to bring you down.’

Compensation was provided to this patient for the time required for this interview.

The full interview can be viewed here.

IN-DEPTH : THE GLOBAL EPIDEMIOLOGY OF THALASSEMIA

Providing an in-depth analysis of recent publications

Thalassemia is a rare disease, and so global prevalence of the thalassemias, and α-thalassemia in particular, have not been well characterized. Despite the data scarcity, it is becoming clear that the global epidemiology of thalassemia is changing.

Thalassemia has historically been associated with areas of the Mediterranean and Southeastern Asia that had widespread malaria. Thalassemia provides protection against malaria, giving rise to genetic selection for the thalassemia mutations in regions where malaria is endemic. Population screening, improved survival rates, and migration, however, have led to a shift in the prevalence and geographical spread of thalassemia. Improvements in screening and management approaches have enabled more affected individuals to reach adulthood. The ease with which people can relocate across large distances in recent years has facilitated the dispersion of thalassemia carriers far from the areas traditionally associated with a high prevalence. Consequently, thalassemia is becoming more common in areas previously not known for the disease, such as Northern Europe and North America.

Understanding of the global prevalence of thalassemia is limited, with population-based prevalence estimates being unavailable for many countries and outdated for others. The Thalassemia International Federation has taken action to remedy this, developing a platform for a global thalassemia registry, and is calling for worldwide collaboration to adopt a standardized reporting of thalassemia cases. A global registry would also provide valuable information on disease burden and management and highlight challenges to the care of thalassemia so action can be taken to address them.

Some of the most recent population-based data are summarized here.

Asia

Thalassemia has historically been highly prevalent in Southeast Asia, where up to 40% of the population are suspected to be genetic carriers.

In 2018, the Malaysian Thalassemia Registry included 7984 patients living with clinically significant forms of thalassemia. The majority of cases were in the east of the country where there is a high indigenous population. The most common diagnosis, affecting just over a third of patients (34.37%) was hemoglobin E/β-thalassemia, closely followed by β-thalassemia major (33.52%). Alpha-thalassemia was grouped with other less common thalassemias, which together accounted for less than 5% of cases. Analysis of Registry data highlighted the decline in the prevalence of thalassemia in Malaysia over the last decade. There were only 74 affected births in 2018 compared with 334 in 2008 (Figure 1).
The carrier rate of α-thalassemia in Southeastern Asia was recently reported to be 22.6%, but it should be noted that the systematic review from which this figure was calculated included some non-population based analyses. Of the Asian countries studied, Malaysia had the lowest rate (17.3%) compared with 51.5% in Vietnam and 39.5% in Cambodia. Geo-population modelling for Thailand as part of a large Southeast Asia project suggests that the prevalence of α-thalassemia may be greater than historically thought.

Thalassemia has not historically been present in Northeastern Asia, but cases in this region are becoming more common. Analysis of the Korean National Health Insurance database published in 2022 revealed an increase in the prevalence of thalassemia from 0.74/100,000 in 2006 to 2.76/100,000 in 2018. Much of the increase occurred between 2016 and 2018 when the incidence rate almost doubled (0.22/100,000 in 2016, 0.41/100,000 in 2018). Prevalence of thalassemia increased with increasing age within the Korean population, reflecting the effectiveness of early management strategies in extending survival.

### Europe

Until recently, thalassemia in Europe was only considered likely within populations of the Southernmost regions of Italy and Greece. Indeed, Greece has been historically associated with a relatively high prevalence. Analysis of The National Registry for Hemoglobinopathies in Greece from 2010-2015 (N=4032) reported 213 cases of α-thalassemia and 2759 cases of β-thalassemia. However, compared to the previous analysis of the database, there had been a reduction in both the total number of hemoglobinopathy diagnoses and the number of affected births.

In contrast, the prevalence of thalassemia in other Mediterranean countries not traditionally associated with thalassemia appear to have increased. Analysis of data held in the Spanish Registry of Hemoglobinopathies for 2014-2017 identified 75 cases of thalassemia, 62 of which were thalassemia major, and 13 cases of thalassemia intermedia. These reported cases likely underestimate country-wide prevalence, as the registry only recently extended its remit from a pediatric registry to begin enrolling adults.

These limitations highlight the need for further epidemiology studies to better understand the prevalence in Spain.

Cases of thalassemia are now also being reported in Northern Europe. A retrospective cohort analysis of data from National Health Service (NHS) in England for 2009-2018 identified 612 cases of transfusion-dependent β-thalassaemia. More recently, The National Haemoglobinopathy Registry for England 2019/2020 recorded 1744 cases of thalassemia. The vast majority of cases were β-thalassaemia major.

Similarly, analysis of data from the Danish National Patient Register and laboratory database of red blood cell disorders revealed an increase in the prevalence of hemoglobinopathies. The prevalence of α-thalassaemia trait in Denmark increased 41-fold from 2000 to 2015 and β-thalassaemia minor increased eight-fold.

### North America

Current estimates of the prevalence of thalassemia in North America are limited. Retrospective analysis of thalassemia treatment in the US using 2016 data from the MarketScan Commercial and Medicaid Multi-State Database identified 8,480 patients with a diagnosis of β-thalassaemia. As of 2015, California was the only state to have mandatory standardized reporting for α- and β-thalassaemia disorders. At that time, almost 14,000 individuals in California were reported to have a thalassaemia diagnosis and the majority were Asian.

### Take home messages

- Thalassemia is becoming an increasingly global disease due to migration patterns
- Prevalence no longer correlates with endemic malaria
- Prevalence remains high in Southeast Asia and the Mediterranean but is increasing in Northern Europe and North America
- Few data are available for the prevalence of α-thalassemia
- Current prevalence data from population studies are not available for β-thalassaemia in many countries, including the US
- Standardizing thalassemia reporting in a global registry will help to better clarify the global epidemiology

### References

Mitapivat (AG-348) is an oral, small-molecule allosteric activator of red blood cell (RBC) pyruvate kinase (PK) that increases RBC energy metabolism through elevated adenosine triphosphate (ATP) production, which in turn may lead to improvements in RBC maturation, survival, and function. It is in clinical development across a range of hemolytic anemias, including both α-thalassemia and β-thalassemia.

Data from a proof-of-concept phase II trial in non-transfusion-dependent α- or β-thalassemia (NTDT) showed an increase in hemoglobin level (Hb) from baseline in 80.0% (16/20) of patients between Weeks 4 and 12. The average increase in Hb from baseline was 1.3 g/dL.

Phase III studies evaluating the efficacy and safety of mitapivat in patients with α- or β-thalassemia are now underway (NCT04770753, NCT04770779).

More information can be found at https://www.energizeclinicaltrials.com (website for healthcare professionals) and https://www.energizeclinicaltrials.com/hcp/energize-t (website for patients).

**Phase III ENERGIZE trial (NCT04770753; 2021-000211-23)**

**Design**

ENERGIZE is a phase III, randomized, double-blind trial evaluating the efficacy and safety of mitapivat relative to placebo in patients with NTDT. Eligible patients will have α- or β-thalassemia, have received ≤5 RBC units during the previous 24 weeks and not needed RBC transfusions for ≤8 weeks, be aged ≥ 18 years, and have Hb ≤10.0 g/dL (estimated N=171).

Mitapivat 100 mg or matching placebo (2:1 randomization) will be administered twice daily for 24 weeks. Patients completing the 24-week study period can continue in the open-label extension to receive mitapivat for up to an additional 5 years.

The primary endpoint of the ENERGIZE trial is the proportion of patients in whom Hb increases by ≥1.0 g/dL from baseline between Week 12 and Week 24. Secondary endpoints include change from baseline in mean Hb, change from baseline in mean fatigue subscale score of the Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue) scale from Week 12 to Week 24, and markers of hemolysis and erythropoiesis.

**Latest trial status**

As of 9/14, this global trial has 38 study sites open and is estimated to complete in December 2023.

**Phase III ENERGIZE-T trial (NCT04770779; 2021-000212-34)**

**Design**

ENERGIZE-T is a phase III, randomized, double-blind trial evaluating the impact of mitapivat on transfusion burden compared with placebo in patients (estimated N=240) with transfusion-dependent thalassemia (TDT). Eligible patients will be ≥18 years old and have α- or β-thalassemia requiring transfusion of 6 to 20 RBC units and a ≤6-week transfusion-free period during the 24 weeks prior to enrolling.

Mitapivat 100 mg or matching placebo (2:1 randomization) will be administered twice daily for 48 weeks. Patients completing the 48-week double-blind intervention phase can continue in the open-label extension phase to receive mitapivat for up to an additional 5 years.

The primary endpoint of the ENERGIZE-T trial is the proportion of patients who achieved a ≥50% reduction in transfused RBC units during any consecutive 12-week period. Secondary endpoints include the proportion of patients with ≥50% reduction from baseline in transfused RBC units during any consecutive 24-week period and change from baseline in number of RBC units transfused from Week 13 to Week 48.

**Latest trial status**

As of 9/14, this trial has 42 study sites open for recruitment and is estimated to complete in June 2024.
Planned study sites for ENERGIZE and ENERGIZE-T

References
2. A Study Evaluating the Efficacy and Safety of Mitapivat in Participants with Non-Transfusion-Dependent Alpha- or Beta-Thalassaemia (α- or β-TDT) (ENERGIZE). ClinicalTrials.gov Identifier: NCT04770753.
3. A Study Evaluating the Efficacy and Safety of Mitapivat in Participants with Transfusion-Dependent Alpha- or Beta-Thalassaemia (α- or β-TDT) (ENERGIZE-T). ClinicalTrials.gov Identifier: NCT04770779.

The following experts are involved in this initiative
- Khaled Musallam, MD, PhD
- Sujit Sheth, MD
- Thomas Coates, MD
- Vip Viprakasit, MD, DPhil
- Ali Taher, MD, PhD
- Hanny Al-Samkari, MD
- Kevin Kuo, MD
- Maria Dominica Cappellini, MD

Mitapivat is not approved for the treatment of thalassemia by any health authority. The safety and efficacy of mitapivat in thalassemia are under investigation and have not been established. There is no guarantee that mitapivat will receive health authority approvals or become commercially available in any country for the uses under investigation.

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KEY DATES

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<tr>
<th>Date</th>
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<tr>
<td>October 17-20, 2022</td>
<td>Eleventh Cooley’s Anemia Symposium, New York, NY, USA</td>
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<tr>
<td>October 20-22, 2022</td>
<td>17th Annual Sickle Cell and Thalassemia Conference (ASCAT), London, UK</td>
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<td>December 10-13, 2022</td>
<td>64th ASH Annual Meeting, New Orleans, LA, USA</td>
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<td>April 27-29, 2023</td>
<td>International Summit on Hematology and Blood disorders</td>
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<td>May 8, 2023 12:00 AM - May 9, 2023 12:00 AM</td>
<td>World Thalassemia Day</td>
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<td>June 8-11, 2023</td>
<td>European Hematology Association (EHA) Congress, Hybrid and Frankfurt, Germany</td>
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